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(21) International Application Number: PCT/US91/02668 (22) International Filing Date: 18 April 1991 (18.04.91) (30) Priority data: 522,922 19 April 1990 (19.04.90) US (60) Parent Application or Grant (63) Related by Continuation US 522,922 (CIP) Filed on 19 April 1990 (19.04.90) (71) Applicants (for all designated States except US): MEDIMUNE, INC. [US/US]; 19 Firstfield Road, Gaithersburg, MD 20878 (US). HENRY M. JACKSON FOUNDATION FOR THE ADVANCEMENT OF MILITARY MEDICINE [US/US]; 11426 Rockville Pike, Rockville, MD 20852 (US).		(72) Inventors; and (75) Inventors/Applicants (for US only) : YOUNG, James, F. [US/US]; 12624 Gravenhurst Lane, Gaithersburg, MD 20878 (US). PRINCE, Gregory, A. [US/US]; 14800 Pettit Way, Potomac, MD 20854 (US). (74) Agents: OLSTEIN, Elliot, M. et al.; Carella, Byrne, Bain, Gilfillan, Cecchi & Stewart, 6 Becker Farm Road, Roseland, NJ 07068 (US). (81) Designated States: AT (European patent), BE (European patent), CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, LU (European patent), NL (European patent), SE (European patent), US. Published <i>With international search report.</i>
(54) Title: ADMINISTRATION OF MONOCLONAL ANTIBODIES AGAINST RESPIRATORY VIRUSES (57) Abstract A process for the prophylaxis and/or treatment of respiratory viruses which comprises administering topically or systemically, to an animal, at least one monoclonal antibody against at least one respiratory virus. The present invention is particularly applicable to the prophylaxis of respiratory syncytial virus, or RSV, by administering at least one monoclonal antibody against a fusion protein of respiratory syncytial virus.		

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**ADMINISTRATION OF MONOCLONAL ANTIBODIES
AGAINST RESPIRATORY VIRUSES**

This application is a continuation-in-part of Application Serial No. 522,922, filed April 19, 1990.

This invention relates to the prophylaxis and/or treatment of respiratory viruses. More particularly, this invention relates to the prophylaxis and/or treatment of respiratory viruses through the administration of monoclonal antibodies against a respiratory virus.

Walsh, et al., Infect. and Immun., Vol. 43, pgs. 756-758 (Feb. 1984), discloses the intraperitoneal administration of monoclonal antibodies against glycoproteins of respiratory syncytial virus to cotton rats, followed by an intranasal challenge of respiratory syncytial virus three hours after administration of the monoclonal antibody. Such treatment with the monoclonal antibodies resulted in the reduction of viral titers or in the absence of virus in the lungs of the cotton rats which were given the monoclonal antibodies, while virus was detected in the lungs of all rats in the control group. The treated group of rats also showed a decrease in virus growth in nasal turbinates.

USSR Patent No. 745,523 (1978) discloses the intranasal administration of secretory IgA antibodies, isolated from female colostrum, to a group of infants in a children's hospital, prior to an outbreak of respiratory syncytial virus. Those infants who were given the antibodies prior to the outbreak contracted less severe cases of respiratory syncytial virus and had developed fewer complications associated with the virus, than those infants who were not administered the antibodies.

U.S. Patent No. 4,800,078, issued to Prince, et al. discloses a method of treating respiratory disease caused by respiratory syncytial virus (RSV) by topically administering RSV antibodies into the lower respiratory tract. The antibodies are administered as a purified human gamma globulin, and may be administered in an amount of from about 0.025 to 0.05g/kg of body weight. The purified human gamma globulin preparation may contain RSV neutralizing antibodies at a titer greater than 1:2,000.

In accordance with an aspect of the present invention, there is provided a process for the prophylaxis of at least one respiratory virus in an animal comprising topically administering to the animal at least one monoclonal antibody against the at least one respiratory virus.

Preferably, the at least one monoclonal antibody is administered to the respiratory tract. Such administration may be by intranasal administration or by breathing an aerosol containing said at least one monoclonal antibody. In another preferred embodiment, the animal is a human animal.

In one embodiment, the at least one monoclonal antibody is also a neutralizing antibody.

Representative respiratory viruses include respiratory syncytial viruses, or RSV, parainfluenza viruses (types 1, 2, and 3), influenza A viruses, influenza B viruses, and adenoviruses. In one embodiment, the at least one respiratory virus is a respiratory syncytial virus, and the monoclonal antibody or antibodies administered are preferably against a fusion protein of RSV.

Representative examples of monoclonal antibodies against a fusion protein of respiratory syncytial virus include MAb 1436C, MAb 1153, MAb 1142, MAb 151, MAb 1200, MAb 1214, MAb 1237, MAb 1129, MAb 1121, MAb 1107, MAb 13-1, MAb 43-1, MAb 1112, MAb 1269, MAb 1243, MAb 1331H, MAb 1308F, MAb 1302A. Such antibodies are neutralizing antibodies. Particularly preferred monoclonal antibodies are MAb 1121, MAb 1129, MAb 1142, MAb 1153, MAb 1243, MAb 1302A, MAb 1308F, and MAb 1331H. It is also contemplated that a mixture of such monoclonal antibodies as hereinabove described may be employed in the prophylaxis of respiratory syncytial virus. These antibodies have been characterized with regard to their neutralizing potential, both to parental RSV strains used to immunize mice to generate these antibodies, as well as a number of different virus strains isolated from 1956 to 1985 from various geographical locations. These antibodies have also been mapped by competitive binding and reactivity profiles of virus escape mutants to three broad antigenic sites (A, B, and C) containing 16 distinct epitopes. Epitopes within antigenic sites A and C show the least variability in natural isolates. Such monoclonal antibodies are further described in Beeler, et al., J. Virol., Vol. 63, No. 7, pgs. 2941-2950 (July, 1989).

Representative examples of non-neutralizing monoclonal antibodies against a fusion protein of respiratory syncytial virus include MAb 1224-1, MAb 1175-40, MAb 1105-1, MAb 1219-22, MAb 1228-28, and MAb 1113-44. These monoclonal antibodies do not neutralize virus infectivity in vitro; however, these antibodies prevent virus replication in cells in vivo. These antibodies may be obtained from Dr. Judy A. Beeler, of the

Laboratory of Infectious Diseases, National Institutes of Allergy and Infectious Diseases, Bethesda, Maryland 20892.

Representative monoclonal antibodies against parainfluenza viruses include MAb 271/7, MAb 170/7, MAb 423/4, MAb 61/5, MAb 403/7, MAb 77/5, MAb 447/12, MAb 101/1, MAb 128/9, MAb 454/11, MAb 149/3, MAb 429/5, MAb 66/4, MAb 68/2, MAb 451/4 and MAb 166/11. Such monoclonal antibodies recognize one of 10 epitopes of the hemagglutinin-neuraminidase (HN) protein of human parainfluenza Type 3 virus. These monoclonal antibodies are further described in Coelingh, et al, Virology, Vol. 143, pgs 569-582 (1985).

Representative monoclonal antibodies against influenza A viruses include MAb 22/1, MAb70/1, MAb 110/1, MAb 264/2, MAb W18/1, MAb 14/3, MAb 24/4, MAb 47/8, MAb 198/2 and MAb 215/2. These monoclonal antibodies are further described in Webster, et al., Virology, Vol. 96, pgs 258-264 (1979). Further examples of monoclonal antibodies against influenza A virus include monoclonal antibodies H2/6A5, H3/4C4, H2/6C4, H2/4B3, H9/B20, H2/4B1, and PEG-1. These monoclonal antibodies are further described in Laver, et al. Proc. Nat. Acad. Sci., Vol 76, No. 3, pgs. 1425-1429 (March 1979). The hereinabove described monoclonal antibodies react against the hemagglutinin protein or the neuraminidase protein of influenza A virus.

Representative monoclonal antibodies against influenza B viruses include monoclonal antibodies 113/2, 124/4, 128/2, 134/1, 146/1, 152/2, 160/1, 162/1, 195/3, 206/2, 238/4, and 280/2. The monoclonal antibodies react against the hemagglutinin protein of influenza B virus. Such

monoclonal antibodies are further described in Oxford, et al., J. Gen. Virol., Vol. 64, pgs 2367-2377 (1983).

Representative monoclonal antibodies against adenoviruses include monoclonal antibodies 5Hx-1, 5Hx-2, 5Hx-3, 5Hx-4, 5Hx-5, 5.100K-1, 5PB-1, and 5Fb-1. Monoclonal antibodies 5Hx-1, 5Hx-2, 5Hx-3, 5Hx-4, and 5Hx-5 were found to react against the hexon polypeptide of adenovirus type 5. Monoclonal antibody 5.100K-1 was found to react against the 100K polypeptide of adenovirus type 5. Monoclonal antibody 5PB-1 was found to react against the penton base polypeptide of adenovirus type 5, and monoclonal antibody 5Fb-1 was found to react against the fibre polypeptide of adenovirus type 5. Such monoclonal antibodies are further described in Russell, et al., J. Gen. Virol., Vol. 56, pgs. 393-408 (1981).

It is also contemplated, that within the scope of the present invention, a mixture of monoclonal antibodies may be administered against more than one type of respiratory virus. For example, one may administer at least one monoclonal antibody against a respiratory syncytial virus and at least one monoclonal antibody against parainfluenza Type 3 virus for the prophylaxis of respiratory syncytial virus and parainfluenza Type 3 virus. It is to be understood that other combinations of monoclonal antibodies may be administered as well, with such combinations depending upon the combination of respiratory viruses one wishes to prevent.

The at least one monoclonal antibody, when administered to the respiratory tract, either intranasally or by breathing an aerosol

containing said at least one monoclonal antibody, is administered in an amount of from about 10 μ g to about 250mg, preferably of from about 5mg to about 125mg.

In accordance with another aspect of the present invention, there is provided a process for the prophylaxis of at least one respiratory virus in an animal, preferably a human animal, which comprises intramuscularly administering to the animal at least one monoclonal antibody against the at least one respiratory virus. The at least one respiratory virus may be selected from those hereinabove described, and the monoclonal antibody or antibodies which may be administered, may be selected from those hereinabove described as well.

The at least one monoclonal antibody, when administered intramuscularly, is administered in an amount of from about 1mg to about 250mg, preferably from about 5mg to about 100mg. One monoclonal antibody, or a mixture of monoclonal antibodies against one or more respiratory viruses, may be administered.

In accordance with another aspect of the present invention, there is provided a process for the treatment of at least one respiratory virus in an animal, which comprises administering to the animal at least one monoclonal antibody against the at least one respiratory virus. The at least one respiratory virus may be selected from those hereinabove described, and the monoclonal antibody or antibodies which may be administered, may be selected from those hereinabove described as well. One monoclonal antibody, or a mixture of monoclonal antibodies against one or more respiratory viruses may be administered.

The at least one monoclonal antibody may be administered topically or systemically. Examples of topical administration include intranasal administration, or administration by breathing an aerosol containing the at least one monoclonal antibody. Examples of systemic administration include intramuscular administration and intravenous administration.

The at least one monoclonal antibody, when administered topically, is administered to the animal in an amount of from about 10 μ g to about 500mg preferably of from about 5mg to about 250mg. When administered systemically, the at least one monoclonal antibody is administered in an amount of from about 1mg to about 250mg, preferably from about 5mg to about 100mg.

The at least one monoclonal antibody, whether administered topically or systemically, and whether administered for the prophylaxis or treatment of at least one respiratory virus, preferably is administered in conjunction with a suitable amount of a pharmaceutical carrier. Examples of suitable pharmaceutical carriers include isotonic solutions such as 5% dextrose or 0.9% saline. If a lyophilized preparation is desired, stabilizers such as 0.25M glycine, 10% maltose or 10% sucrose may be included.

The invention will now be described with respect to the following examples; however, the scope of the present invention is not intended to be limited thereby.

Example 1

Eight different monoclonal antibodies, each of which is specific for RSV fusion protein (F glycoprotein), were tested for their ability to block RSV replication when administered to cotton rats by the intranasal route prior to the virus challenge. These antibodies represent seven different epitopes, reacted with at least 13 of 14 virus isolates tested, and retained the greatest neutralizing activity against virus escape mutants selected with the other antibodies. The features of each of the eight antibodies are summarized in Table I below.

Table I

<u>Monoclonal Antibody</u>	<u>Antigenic Site</u>	<u>Epitope</u>	<u>Immunoglobulin Subclass</u>	<u># of RSV Strains Neutralized</u>
1153	A	1	IgG ₁ K	13/14
1142	A	1	IgG ₁ K	13/14
1129	A	4	IgG ₁ K	13/14
1121	A	5	IgG ₁ K	13/14
1243	C	11	IgG _{2A} K	13/14
1331H	C	12	IgG _{2A} K	14/14
1308F	C	13	IgG ₁ K	14/14
1302A	C	14	IgG ₁ K	14/14

Cotton rats (*S. fulviventris*), in groups of three rats each, average weight 100 grams, were anesthetized with methoxyflurane and given 0.1ml of an antibody solution at a concentration of 10mg/ml or 1mg/ml in phosphate buffered saline (PBS) by intranasal (i.n.) instillation. The antibody was one of the eight monoclonal antibodies hereinabove described, or a pooled mixture of all eight monoclonal antibodies (10mg/ml total, 1.25mg/ml each or 1mg/ml total, 0.125mg/ml each), or standard human immune globulin (Sandoglobulin, Sandoz, Inc., East Hanover,

N.J.). Control rats were given 0.1ml of a bovine serum albumin (BSA) suspension (10mg/ml or 1mg/ml) in PBS.

One day later, animals were again anesthetized with methoxyflurane and challenged by i.n. instillation of $10^{5.0}$ plaque forming units (PFU) of the Long strain of RSV. Four days after virus challenge, all animals were sacrificed by carbon dioxide asphyxiation. Lungs were harvested and homogenized in 10 parts (wt/vol) of Hanks balanced salt solution supplemented with 0.218 M sucrose, 4.4 mM glutamate, 3.8 mM KH_2PO_4 and 3.2 mM K_2HPO_4 and the resulting suspension was stored at -70°C until assayed for virus content. Virus titers were determined using a plaque assay on HEP-2 cell monolayers as disclosed by Prince, et al., Am. J. Pathol., Vol. 93, pgs. 771-792 (1978) and are expressed as PFU per gram of tissue. The virus titers for each preparation administered are shown in Figure 1.

Each of the monoclonal antibodies showed a significant reduction in pulmonary virus titer, and were at least as effective and in most cases more effective than the standard immune globulin or the pool of the eight monoclonal antibodies. Five of the eight monoclonal antibodies appear to prevent infection at the high dose (10mg/ml) and one (1331H) even at the low dose (1mg/ml).

Example 2

Cotton rats (*S. fulviventris*) in groups of three rats each, average weight 100 grams, were injected with 0.1ml in each flank (0.2ml total) of bovine serum albumin (BSA), or 0.1ml in each flank (0.2ml total) of

either MAb 1129 or MAb 1331H. The monoclonal antibodies are at a concentration of 10mg/ml. One day later, the rats were anesthetized with methoxyflurane and challenged by intra-nasal instillation of $10^{5.0}$ PFU of the Long Strain of RSV. Four days after the virus challenge, the rats were sacrificed by carbon dioxide asphyxiation, the lungs were harvested, and the virus content was determined. As shown in Figure 2, there was a significant reduction in pulmonary virus titers in rats treated with either of the monoclonal antibodies as compared with the BSA treated rats.

Example 3

Cotton rats (*S. fulviventor*) in groups of three rats each, average weight 100 grams, were anesthetized with methoxyflurane and challenged with $10^{5.0}$ PFU of the Long strain of RSV. Three days later, the animals were anesthetized with methoxyflurane and given 0.1ml of a solution of MAb 1129 or MAb 1331H (10mg/ml) in PBS, or of bovine serum albumin (10mg/ml) in PBS. Administration was by intranasal instillation. The animals were sacrificed the next day by carbon dioxide asphyxiation, the lungs were harvested, and the virus content was determined. As shown in Figure 3, a significant reduction in pulmonary virus titers of animals treated with either of the monoclonal antibodies as compared to the BSA-treated animals was observed.

Example 4

The eight monoclonal antibodies described above in Example 1 were further examined for their ability to block RSV replication when administered to cotton rats by the intranasal route prior to virus challenge. Cotton rats (*S. hispidus*, 4 animals per group, average weight 100 grams) were anesthetized with methoxyflurane and given 0.1 ml of antibody solution (1 mg/ml, 0.1 mg/ml or 0.01 mg/ml in phosphate-buffered saline (PBS)) by intranasal (i.n.) instillation. Control animals were given 0.1 ml of a bovine serum albumin suspension (1 mg/ml) in PBS. One day later, animals were again anesthetized with methoxyflurane and challenged by intranasal instillation of $10^{5.0}$ plaque forming units (PFU) of the Long strain of RSV. Four days after virus challenge, all animals were sacrificed by carbon dioxide asphyxiation. Lungs were harvested and homogenized in 10 parts (wt/vol) of Hanks balanced salt solution supplemented with 0.218 M sucrose, 4.4 mM glutamate, 3.8 mM KH_2PO_4 and 3.2 mM K_2HPO_4 and the resulting suspension was stored at -70°C until assayed for virus content. Virus titers were determined using a plaque assay on HEP-2 cell monolayers as disclosed by Prince, et al., Am. J. Pathol., Vol. 93, pgs. 771-792 (1978) and are expressed as PFU per gram of tissue.

Figure 4 shows that each of the monoclonal antibodies, except MAb 1243, showed a significant reduction in pulmonary virus titer when given at the 0.1 mg or 1 mg doses.

Example 5

Neutralizing monoclonal antibodies (MAbs) reactive with the F protein of RSV were examined for effectiveness in blocking RSV replication when combined and administered to cotton rats. MAbs 1121 and 1302A were mixed in equal amounts. Cotton rats (*S. hispidus*, 4 animals per group, average weight 100 grams) were anesthetized with methoxyflurane and given 0.1 ml of antibody solution, either the mixture or the individual antibodies at 1 mg/ml, 0.1 mg/ml or 0.01 mg/ml in phosphate-buffered saline (PBS) by intranasal (i.n.) instillation. Control animals were given 0.1 ml of a bovine serum albumin solution (1 mg/ml) in PBS. One day later, animals were again anesthetized with methoxyflurane and challenged by i.n. instillation of $10^{5.0}$ plaque forming units (PFU) of the Long strain of RSV. Four days after virus challenge, all animals were sacrificed by carbon dioxide asphyxiation. Lungs were harvested and homogenized in 10 parts (wt/vol) of Hanks balanced salt solution supplemented with 0.218 M sucrose, 4.4 mM glutamate, 3.8 mM KH_2PO_4 and 3.2 mM K_2HPO_4 and the resulting suspension was stored at -70°C until assayed for virus content. Virus titers were determined using a plaque assay on HEp-2 cell monolayers as disclosed by Prince et al (1978) and are expressed as PFU per gram of tissue.

Figure 5 shows that MAbs 1121 and 1302A when combined together are more effective in reducing viral titers as compared to their individual effects even at a total concentration of 0.01 mg/ml.

Example 6

Six non-neutralizing MABs, reactive with the F protein of RSV were examined for their ability to block RSV replication when administered to cotton rats by the intranasal route prior to challenge with virus. Cotton rats (*S. hispidus*, 4 animals per group, average weight 100 grams) were anesthetized with methoxyflurane and given 0.1 ml of antibody solution, at 10 mg/ml in phosphate-buffered saline (PBS) by intranasal (i.n.) instillation. Control animals were given 0.1 ml of a bovine serum albumin solution (10 mg/ml) in PBS. One day later, animals were again anesthetized with methoxyflurane and challenged by i.n. instillation of $10^{5.0}$ plaque forming units (PFU) of the Long strain of RSV. Four days after virus challenge, all animals were sacrificed by carbon dioxide asphyxiation. Lungs were harvested and homogenized in 10 parts (wt/vol) of Hanks balanced salt solution supplemented with 0.218 M sucrose, 4.4 mM glutamate, 3.8 mM KH_2PO_4 and 3.2 mM K_2HPO_4 and the resulting suspension was stored at -70°C until assayed for virus content. Virus titers were determined using a plaque assay on HEP-2 cell monolayers as disclosed by Prince et al (1978) and are expressed as PFU per gram of tissue.

As shown in Figure 6, these non-neutralizing antibodies were effective in significantly decreasing pulmonary viral titers in treated animals even though they do not neutralize virus infectivity in vitro.

It is to be understood, however, that the scope of the present invention is not to be limited to the specific embodiments described above. The invention may be practiced other than as particularly described and still be within the scope of the accompanying claims.

WHAT IS CLAIMED IS:

1. A process for the prophylaxis of at least one respiratory virus in an animal, comprising:

topically administering to said animal at least one monoclonal antibody against said at least one respiratory virus.

2. The process of Claim 1 wherein said at least one monoclonal antibody is administered to the respiratory tract.

3. The process of Claim 2 wherein said at least one monoclonal antibody is administered intranasally.

4. The process of Claim 2 wherein said at least one monoclonal antibody is administered through the breathing of an aerosol containing said at least one monoclonal antibody.

5. The process of Claim 1 wherein said at least one respiratory virus is selected from the group consisting of respiratory syncytial viruses, parainfluenza viruses, influenza A viruses, influenza B viruses, and adenoviruses.

6. The process of Claim 5 wherein said at least one respiratory virus is a respiratory syncytial virus.

7. The process of Claim 6 wherein said at least one monoclonal antibody is against a fusion protein of a respiratory syncytial virus.

8. The process of Claim 7 wherein said at least one monoclonal antibody is selected from the group consisting of MAb 1436C, MAb 1153, MAb 1142 MAb 151, MAb 1200, MAb 1214, MAb 1237, MAb 1129, MAb 1121, MAb 1107, MAb 13-1, MAb 43-1, MAb 1112, MAb 1269, MAb 1243, MAb 1331H, MAb 1308F, and MAb 1302A.

9. The process of Claim 7 wherein said at least one monoclonal antibody is selected from the group consisting of MAb 1224-1, MAb 1175-40, MAb 1105-1, MAb 1219-22, MAb 1228-28, and MAb 1113-44.

10. The process of Claim 8 wherein a mixture of at least two of said monoclonal antibodies are administered.

11. The process of Claim 2 wherein said at least one monoclonal antibody is administered in an amount of from about 10 μ g to about 250mg.

12. The process of Claim 11 wherein said at least one monoclonal antibody is administered in an amount of from about 5mg to about 125mg.

13. A process for the prophylaxis of at least one respiratory virus in an animal, comprising:

intramuscularly administering to said animal at least one monoclonal antibody against said at least one respiratory virus.

14. The process of Claim 13 wherein said at least one monoclonal antibody is administered in an amount of from about 1mg to about 250mg.

15. The process of Claim 14 wherein said at least one monoclonal antibody is administered in an amount of from about 5mg to about 100mg.

16. A process for the treatment of at least one respiratory virus in an animal, comprising:

administering to said animal at least one monoclonal antibody against said at least one respiratory virus.

17. The process of Claim 16 wherein said at least one monoclonal antibody is administered topically.

18. The process of Claim 17 wherein said at least one monoclonal antibody is administered in an amount of from about 10 μ g to about 500mg.

19. The process of Claim 18 wherein said at least one monoclonal antibody is administered in an amount of from about 5mg to about 250mg.

20. The process of Claim 16 wherein said at least one monoclonal antibody is administered systemically.

21. The process of Claim 20 wherein said at least one monoclonal antibody is administered in an amount of from about 1mg to about 250mg.

22. The process of Claim 21 wherein said at least one monoclonal antibody is administered in an amount of from about 5mg to about 100mg.

23. A topical composition for the prophylaxis of at least one respiratory virus, comprising: at least one monoclonal antibody against said at least one respiratory virus; and a pharmaceutically acceptable carrier.

24. An intramuscularly administrable composition for the prophylaxis of at least one respiratory virus, comprising: at least one monoclonal antibody against said at least one respiratory virus; and a pharmaceutically acceptable carrier.

25. A composition for the treatment of at least one respiratory virus, comprising: at least one monoclonal antibody against said at least one respiratory virus; and a pharmaceutically acceptable carrier.

26. The process of Claim 1 wherein a mixture of at least two of said monoclonal antibodies are administered.

27. The process of Claim 13 wherein a mixture of at least two of said monoclonal antibodies are administered.

28. The process of Claim 16 wherein a mixture of at least two of said monoclonal antibodies are administered.

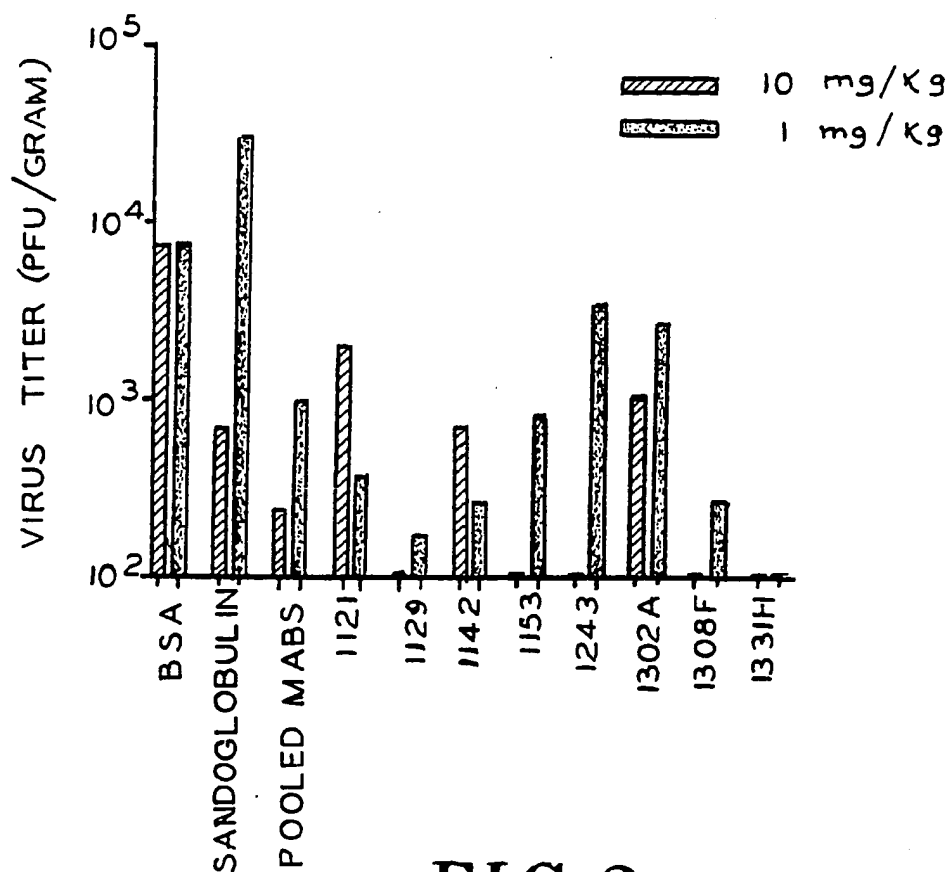
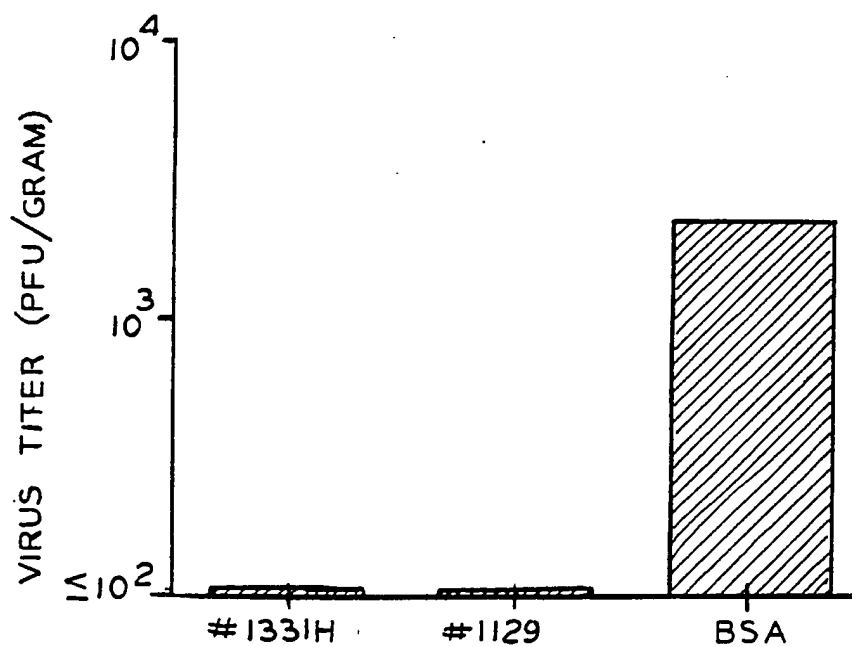
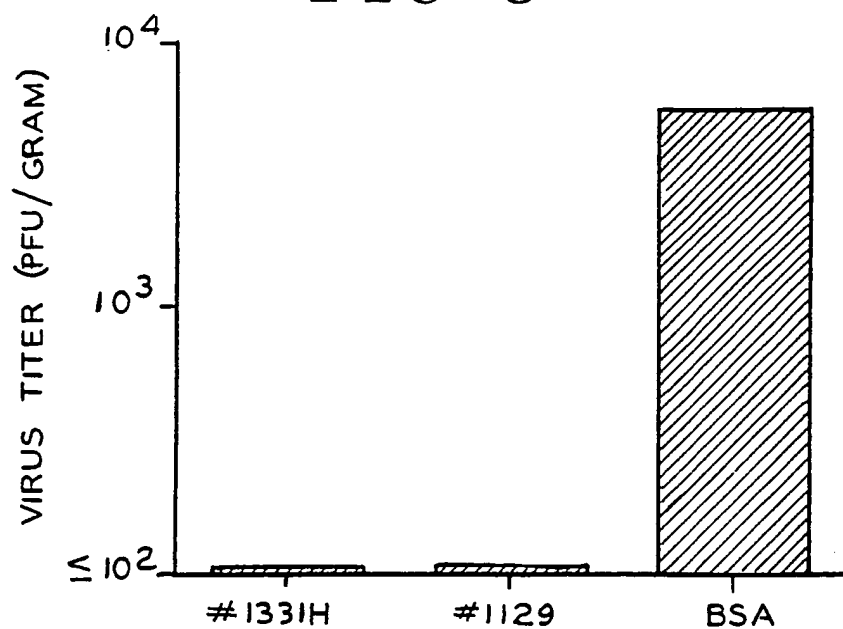
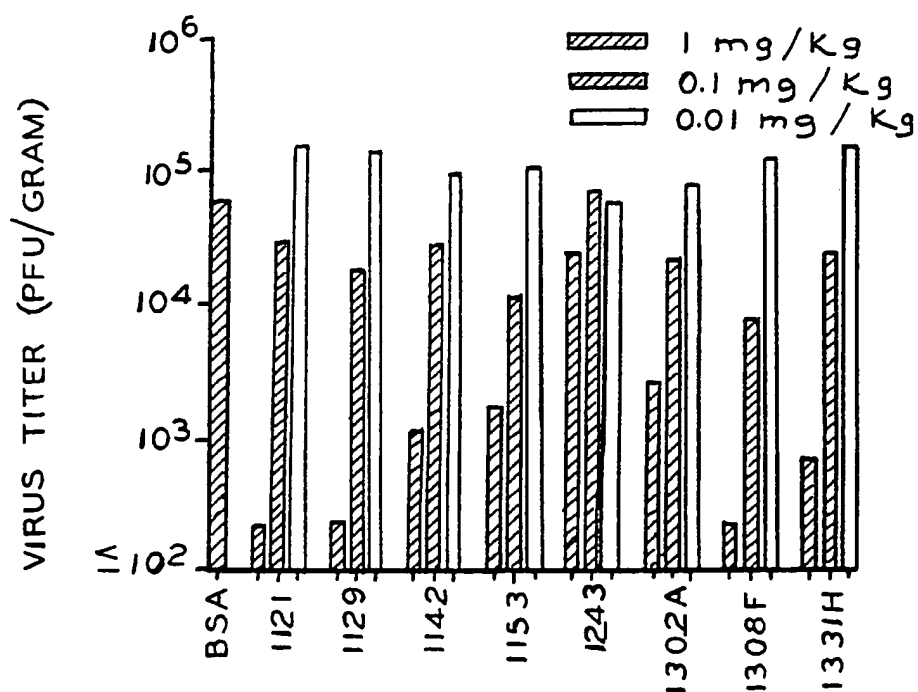
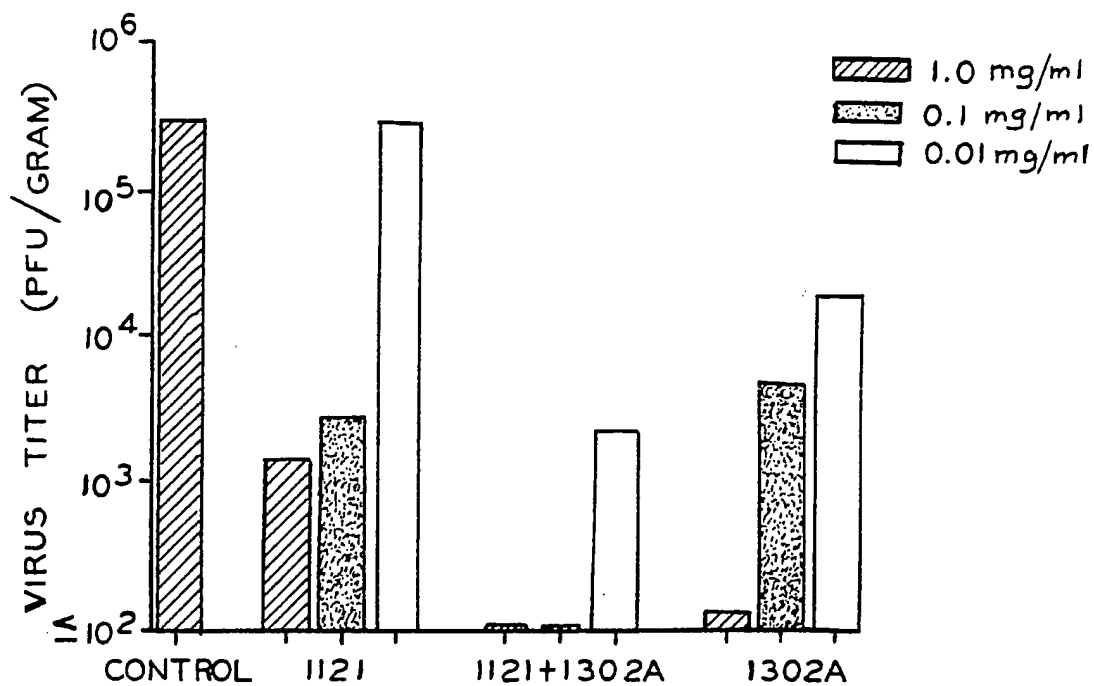
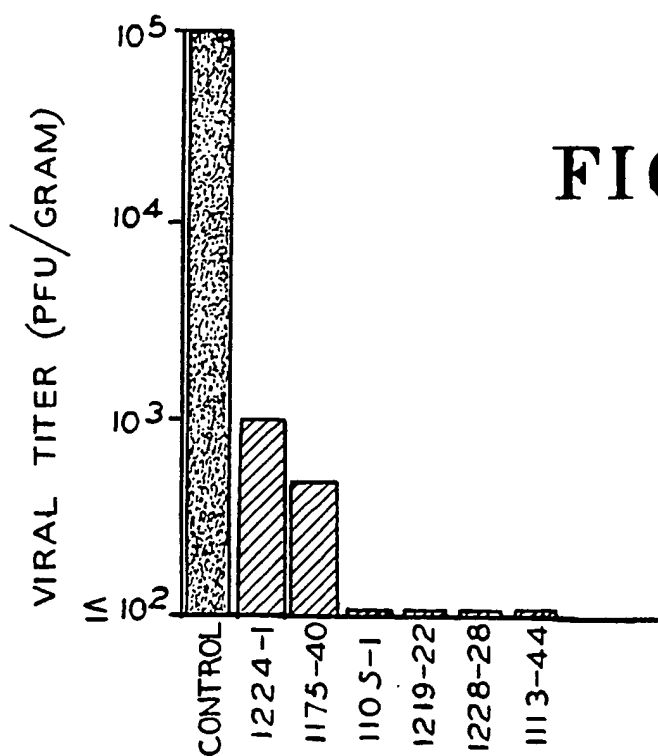
^{1/3}
FIG. 1

FIG. 2



^{2/3}
FIG. 3**FIG. 4**

^{3/3}
FIG. 5**FIG. 6**

SUBSTITUTE SHEET

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US91/02668

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) *

According to International Patent Classification (IPC) or to both National Classification and IPC
IPC(5): A61K 39/42, 39/345
U.S.Cl.: 530/387; 424/85.8

II. FIELDS SEARCHED

Minimum Documentation Searched ⁷

Classification System

Classification Symbols

U.S.Cl.

530/387; 424/85.8

Documentation Searched other than Minimum Documentation
to the Extent that such Documents are Included in the Fields Searched ⁸

APS, DIALOG

III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁹

Category ⁶	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
X Y	The Journal of Infectious Diseases, Volume 152, No. 5, issued November 1985. V.G. Hemming, "Studies of Passive Immunotherapy for Infections of Respiratory Syncytial Virus in the Respiratory Tract of a Primate Model", pages 1083-1087. See entire document.	1-22 1-22
X Y	US,A, 4,800,078 (Prince et al.) 24 January 1989, see entire document.	1-25 1-25
X	Immunology, Volume 52, issued 1984. G. Taylor et al., "Monoclonal antibodies protect against respiratory syncytial virus infection in mice" pages 137-142. See entire document.	1-25

* Special categories of cited documents: ¹⁰

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IV. CERTIFICATION

Date of the Actual Completion of the International Search

08 July 1991

Date of Mailing of the International Search Report

30 JUL 1991

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III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X Y	Journal of Virology, Volume 61, No. 6, issued June 1987, G.A. Prince et al., "Effectiveness of Topically Administered Neutralizing Antibodies in Experimental Immunotherapy of Respiratory Syncytial Virus Infection in Cotton Rats." pages 1851-1854. See entire document.	1-25 1-25
X Y	US,A, 4,719,235 (Kern) 12 January 1988, see entire document.	1-25 1-25
Y,P	US,A, 4,933,169 (Shanbrom) 12 June 1990, see entire document.	1-22
Y,P	US,A, 4,965,069 (Quash et al.) 23 October 1990, see entire document.	1-22
Y	Journal of Virology, Volume 63, No. 2, issued February 1989, R. Garcia-Barreno et al., "Market Differences in the antigenic structure of Human Respiratory syncytial Virus F and G Glycoproteins", pages 925-932. See entire document.	26-28
Y	Journal of Virology, volume 63, No. 1, issued January 1989, K. van Wyke Coelingh et al., "Antigenic and Functional Organization of Human Parainfluenza Virus Type 3 Fusion Glycoprotein", pages 375-382. See entire document.	26-28
Y	Journal of Virology, Volume 62, No. 11, issued November 1988, L. J. Anderson et al., "Neutralization of Respiratory Syncytial virus by Individual and Mixtures of F and G Protein monoclonal antibodies," pages 4232-4238. See entire document.	26-28
Y	Journal of Virology, Volume 55, No. 3, issued September 1985, G.A. Prince et al., "Quantitative aspects of Passive Immunity to Respiratory Syncytial Virus Infection in Infant Cotton Rats", pages 517-520. See entire document.	23-28
Y	US,A, 4,625,015 (Green et al.) 25 November 1986, see entire document.	1-25